Bioorganometallic Chemistry: Supramolecular Host Recognition Processes with Biological Compounds, Organometallic Pharmaceuticals , and Alkali-Metal ions as Guests

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Abstract

Molecular recognition, via non-covalent processes, such as hydrogen bonding, π-π, and hydrophobic interactions, is an important biological phenomenon for guests, such as drugs, proteins, and other important biological molecules with; for example, host DNA/RNA. We will review several novel molecular recognition processes using guests that encompass aromatic and aliphatic amino acids, substituted aromatic carboxylic acids, and aliphatic carboxylic acids with, for example, a supramolecular, bioorganometallic host, the (η^5-pentamethylcyclopentadienyl)rhodium (Cp*Rh)-nucleotide, cyclic trimer complex, [Cp*Rh(2'-deoxyadenosine)]$_3$(OTf)$_3$ (**1**), (OTf = trifluoromethanesulfonate), conducted in aqueous solution at pH 7, utilizing ^{1}H NMR, NOE, and computer docking techniques. The association constants (K_a) and free energies of complexation (ΔG^o) will also be presented, as well as a discussion on the solvophobic effects in H_2O that appear to control the extent of host-guest interaction. Another new molecular recognition process, based on selective H-bonding, was discovered with novel host, *trans*-[(Cp*Rh)$_2$(η^1-(N3)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$, **2**, and several examples of aromatic amino acid guests, L-tryptophan and L-phenylalanine, in water at pH 7.0. Computer docking experiments with the organometallic supramolecular hosts and biological guests were conducted in order to further understand the non-covalent

interactions that are prevalent. New organometallic ionophores, compounds that selectively coordinate alkali metal ions, will be presented both from a synthetic strategy as well as selective hosts for various alkali metal ions. Finally, the estradiol hormone receptor site, which is thought to be the major receptor protein implicated in hormone-dependant breast cancers, afforded the possibility to conduct computer docking/energy minimization experiments at the receptor site to discern the conformation and non-covalent interactions of a potential organometallic pharmaceutical, Ferrocifen, and other organometallic drug derivatives, with the surrounding simplified protein structure. It is clear that bioorganometallic chemistry has captured the imagination of many organometallic chemists, while the topic of host-guest molecular recognition chemistry either with organometallic complexes as hosts and biological compounds/alkali metal ions as guests or large protein receptor sites as hosts, for example, for non-covalent binding of potential organometallic pharmaceuticals, will also be at the forefront of future research.

Introduction

Supramolecular interactions that encompass recognition, reaction, transport, etc., are fundamental phenomena in biological systems that are involved in a number of processes between biologically important molecules, such as double and single strand DNA/RNA with; for example, proteins, drugs, and metal-ion containing probes, to name a few examples.[1] Organic chemists have exploited these interesting phenomena to a very significant extent and many supramolecular hosts have been synthesized to investigate the role of these interactions through the molecular recognition of guests, such as nucleosides, nucleotides, amino acids, peptides, and small organic molecules, by predominately non-covalent hydrogen bonding, π-π, and hydrophobic interactions.[2]

Surprisingly, few molecular recognition studies have been attempted with inorganic or organometallic hosts.[3] A pertinent organometallic example was the macrocyclic organopalladium hosts, synthesized by Loeb et al,[3a] that can recognize nucleobases via simultaneous first- and second-sphere coordination; i. e., σ-donation to Pd and hydrogen bonding to the macrocycle heteroatoms. It is important to note that these latter host-guest chemistry studies were performed in *non-aqueous* media presumably because of the instability of their macrocyclic organometallic hosts in water or their lack of solubility in aqueous solution. As well, chiral metalloporphyrin receptors in organic solvents have also been studied to show preferential binding to amino acids,[3b] while Stang and co-worker synthesized a series of platinium and palladium macrocyclic squares for host-guest complexation using a dihydroxynaphthalene compound as an example, also in organic solvents.[3c] An important review on inorganic and organometallic host-guest chemistry was published by Canary and Gibb.[3h]

Among the limited inorganic or organometallic supramolecular hosts studied,[3] none of them; however, were constructed by incorporating nucleobase, nucleoside, or nucleotide molecules as crucial components of the host framework. Recently, the Fish group[4] reported on the molecular recognition of aromatic and aliphatic amino acid and aromatic and aliphatic carboxylic acid guests with supramolecular Cp*Rh-nucleotide cyclic trimer hosts, such as,**1**, in aqueous solution at pH 7. [4a-d]

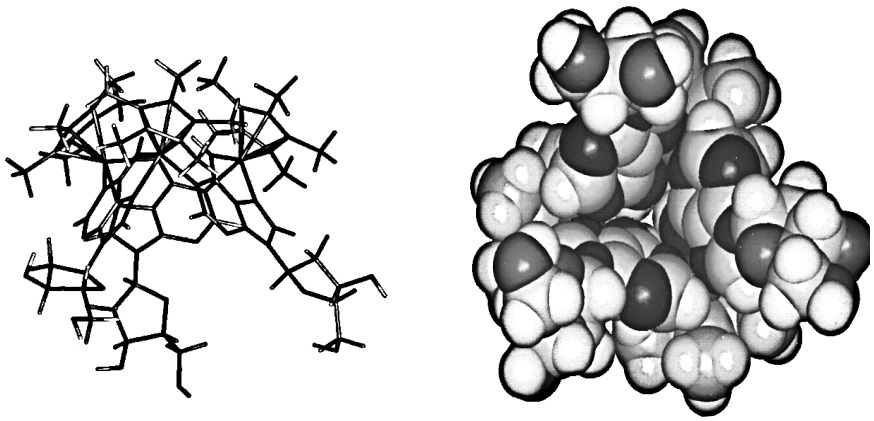


Figure 1: $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTF)_3$, **1**

This type of host-guest chemistry in aqueous solution is important, since it could be considered as the simplest model for the interactions between DNA/RNA molecules and their binding proteins, such as those that regulate genes. Moreover, the non-covalent hydrophobic effect is more fully dramatized in water by solvophobic forces that enhance host-guest interactions.[5]

In this chapter, we will discuss the scope of our molecular recognition studies with two organometallic hosts, by encompassing the guest examples from aromatic and aliphatic amino acids, to substituted aromatic and aliphatic carboxylic acids, and di and tripeptides (Chart 1), while determining the importance of π-π, hydrophobic, and H-bonding effects as a function of

steric, electronic, and conformational parameters, along with host-guest thermodynamic parameters, K_a (association constants) and ΔG^o (free energies of complexation) values. Furthermore, we will also discuss the new supramolecular organometallic complexes that are models for ionophores, biological macrocylic ligands that selectively complex and transport alkali ions, such as Na^+ and Li^+ ions.[6] Finally, hormone receptor proteins that appear to play a key role in the proliferation of breast cancer tumors have been structually characterized via x-ray crystallography, the estrogen receptor, ERα, the estradiol binding site.[4g] Computer docking experiments with organometallic pharmaceuticals show dramatic changes in key helical proteins at the estrogen receptor site, ERα, in comparison to hydroxytamoxifen, the drug of universal use against breast cancer, and these conformational changes will be discussed as they pertain to antagonist and cytotoxic activity.

Hosts 1: Synthesis, Structure, and Aqueous Stability.

Host **1** is shown in Figure 1, the stick model (side view, left) and the CPK model (bottom view, right), while the self-assembly synthetic procedures have been described previously.[4a-d] Trimer **1** is a diastereomeric mixture, while the single-crystal X-ray structure of an enantiomer of the 9-methyladenine cyclic trimer derivative was reported previously, and showed that it has a triangular dome-like supramolecular structure, with three Cp* groups stretching out from the top of the dome, three Me groups pointing to the bottom, three adenine planes forming the surrounding shell, and three Rh atoms embedded in the top of the dome (Figure 2).[4a,d] This molecule also possesses a C3 axis, which passes from the top of the dome to the bottom. The distance between the adjacent methyl groups at the bottom of the dome; i.e., at the opening of this molecular receptor, is about 7.5 Å, while the cavity depth is a

consequence of the substituent on N9 of the nucleobase, nucleoside, or nucleotide and is in the range of ~ 4 Å.

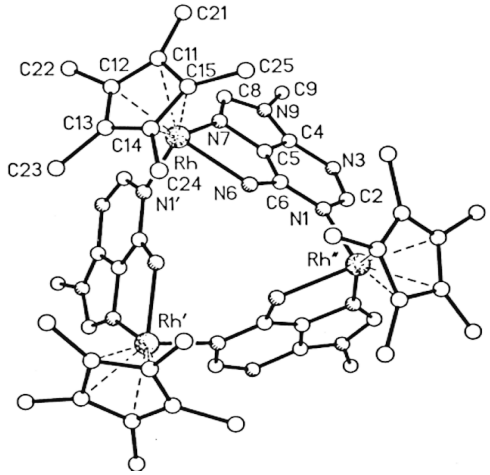


Figure 2**:** X-Ray Structure of [Cp*Rh(μ-η^1(N1):η^2(N6, N7)-9-methyladenine]$_3$(OTf)$_3$.

These Cp*Rh cyclic trimer derivatives are quite stable in aqueous solution; for example, complex **1** was observed by ^{1}H NMR spectroscopy, for two weeks, at pH 6-9, with no apparent decomposition.[4a,b] Therefore, all the critical parameters for host-guest chemistry, such as the supramolecular bowl shape, the large cavity size, and the aqueous stability of these Cp*Rh-nucleobase/nucleoside/nucleotide cyclic trimers provided the opportunity to utilize them as molecular receptors to recognize biologically relevant molecules in aqueous media at a physiological pH of 7.[4a,b]

Molecular Recognition of Aromatic and Aliphatic Amino Acids.

About one half of the twenty common amino acids were selected in this molecular recognition study, and several criteria were considered in the selection process: (1) solubility in H_2O; (2) representativeness; and (3) stability of the hosts in the presence of the amino acids. According to these criteria, tyrosine, cysteine, and methionine were excluded, since the first example is not soluble in H_2O, and the latter two apparently caused the slight decomposition of

the hosts. The structures of the key aromatic and aliphatic amino acids, aromatic and aliphatic carboxylic acids, and di and tripeptides are shown in Chart 1 . The pK_a values of these amino acids are indicative of the zwitterion forms being the predominant species at pH 7.[4a,b,7]

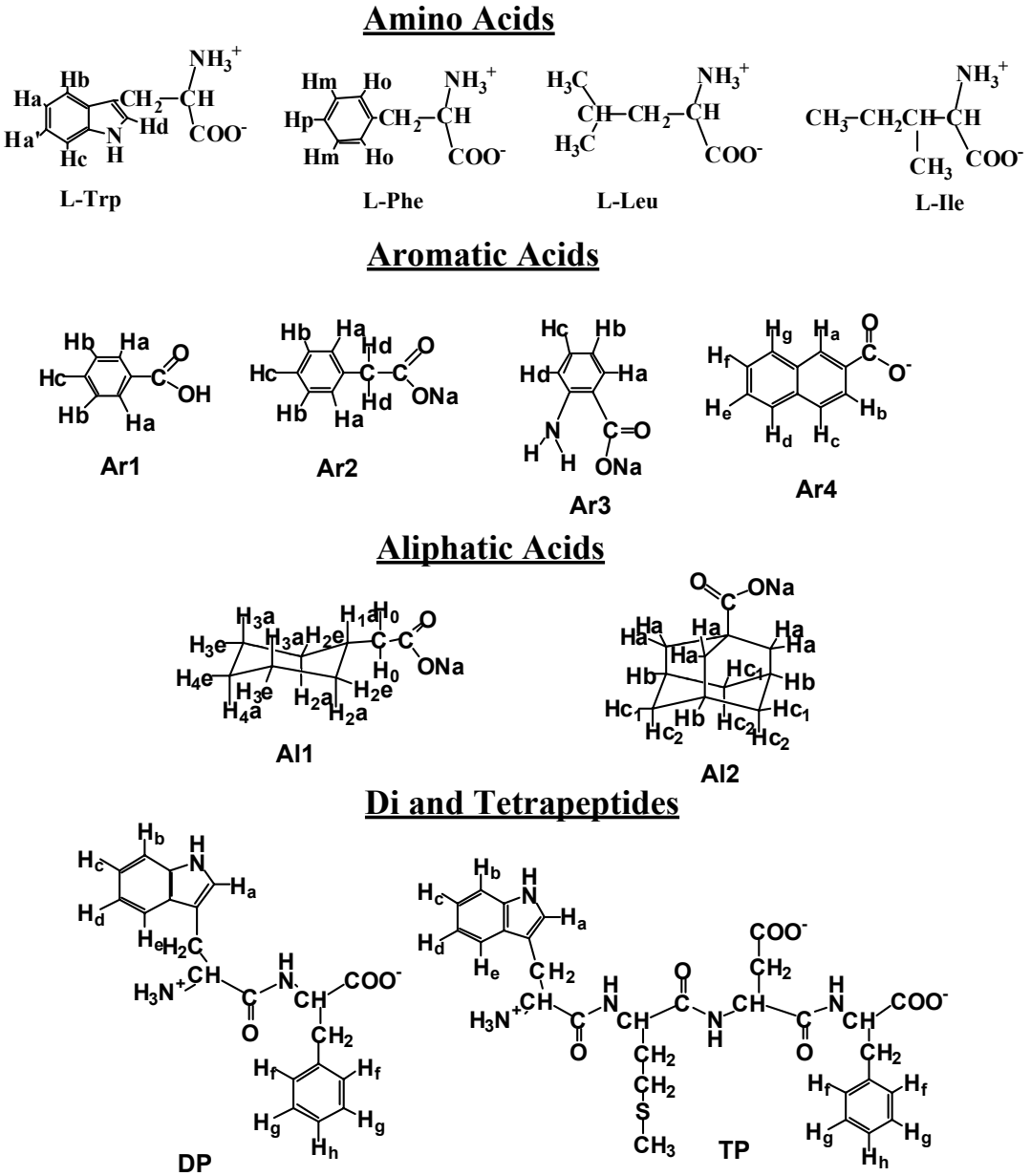


Chart 1: Guests used with host **1** in molecular recognition studies.

The molecular recognition process of these different amino acid guests with host **1** was studied using ^{1}H NMR spectroscopy at ambient temperature.[4a,b] The complexation-induced ^{1}H NMR chemical shifts (CICS) of both guests and amino acid hosts were used to discern non-covalent interactions. The presence of upfield chemical shifts for any guest studied with host **1** was an indication of a possible host-guest interaction. We found that by varying the concentration of the host **1** from 0-1 equivalent in the presence of the appropiate amino acid guest, at a constant concentration of 1.0 equivalents, that the CICS values for the guests were maximized at ~0.8-1.0 equivalents. Therefore, in all subsequent host-amino acid guest experiments, we utilized 1.0 equivalents of each host and 1.2 equivalents of each guest. Furthermore, the data show that cyclic trimer, **1**, can only recognize aromatic amino acids (L-Phe, L-Trp) and several aliphatic amino acids with relatively long hydrophobic side chains (L-Leu, L-Ile), pointing to the possiblity of classical π-π and/or hydrophobic interactions. Other amino acids, such as L-Valine, L-Glycine, L-Histidine, L-Alanine, and L-Proline (not shown in Chart 1); however, do not apparently interact with these hosts. It is important to note that no enantio- or diastereoselectivity was observed by ^{1}H NMR for host **1** in the molecular recognition reactions, and thus, it appears that all stereoisomers were affected in a similar manner.

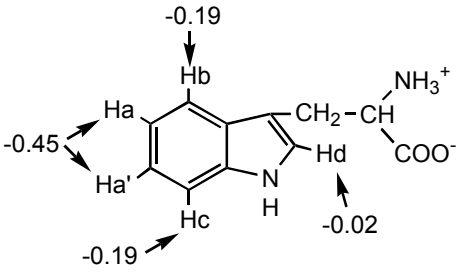
These observations may be rationalized by the following three factors: (1) sterically, the cavity size of host **1** were large enough to fit L-Trp without any significant hindrance, and furthermore, L-Trp entered the cavities by using the most favored steric orientation. It is necessary to note that the major portion of L-Trp, which entered the receptor, was the benzene ring, which was very similar to the L-Phe case and; therefore, the steric influences of L-Trp and L-Phe during the recognition process were about the same; (2) electronically, the lone

electron pair on the nitrogen atom of the five-member heterocyclic ring of L-Trp could donate electron density to the adjacent benzene ring to make this ring more electron-rich in comparison to L-Phe. Presumably, this electron enrichment is one reason that L-Trp has strong π-π interactions with the electron-deficient π system of **1**;[2b,5b] (3) the greater hydrophobicity of L-Trp (solubility = .01g/g H_2O, Hansch partition coefficient, log $P_{octanol}$ = -1.04) appears to be another important reason, with the solvophobic effect of water as the driving force for this rather facile molecular recognition process. The strong interaction of L-Trp with **1** must be multi-component, encompassing π-π, hydrophobic, and solubility effects, since some amino acids, such as L-Ile and L-Leu, have relatively long hydrophobic side chains and were shown to be weakly associated with host **1**; the later mentioned aliphatic amino acid are also more soluble in water in comparison to L-Trp. As well, L-Glycine, which also has a relatively long hydrophilic side chain, apparently did not interact with **1**, and again dramatizes the solvophobic effect.

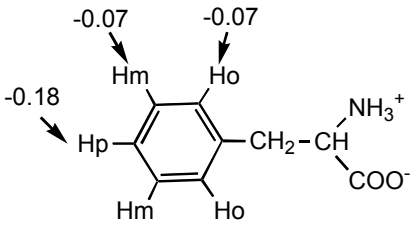
For nucleoside host **1**, the role of the hydroxyl groups on the ribose may be understood by comparing their interactions with guests, L-Phe and L-Trp. Host **1** has one OH group per each ribose unit; and therefore, at the opening of this host cavity, the hydrophobicity increases; a delicate balance of hydrophobicity and hydrophilicity exists. More importantly, the steric hindrance on the sugar of the nucleotide can decrease the non-covalent interactions with guests. For example, three ribose units with two OH groups and a monophosphate methyl ester at the 5' position has the propensity for the surrounding H_2O molecules and to minimize this unfavorable interaction (desolvate) these three ribose units come close to each other, and presumably, this effect tends to increase the steric hindrance at the opening of the host cavity. Alternatively, the two OH groups on each ribose should have relatively favorable interactions

with the surrounding H_2O molecules, and hence less steric demand at the opening of the host cavity. This rationale was supported by comparing the CICS values of L-Phe , which showed the largest value for the least hindered host, and the smallest value for the most hindered host. In the case of L-Trp, the situation is more complicated, since the CICS values of L-Trp with **1** were the greatest. This sequence may be explained by considering the contribution of the hydrophobicity of the host, or hydrophobic effect of the host-guest complexation. As mentioned, L-Trp has greater hydrophobicity than L-Phe, and therefore, the hydrophobic interactions between L-Trp and **1** appears to play an important role during the recognition process, besides the π-π interactions and the steric effect at the opening of the host cavities. With the decreasing number of OH groups on the ribose units, the hydrophobicity increases, but at the same time, the steric hindrance increases as well. These two factors, which have the opposite influences on the recognition process of L-Trp, appear to be responsible for the interaction between **1** and L-Trp being optimal.

The ^{1}H NMR signals of Ha and Ha' on L-Trp were influenced to the greatest extent by host **1**,[1a,2,5b] with a 0.45 ppm upfield shift, while those of the other two protons, Hb and Hc, had significantly smaller upfield-shifts (0.19 ppm). The ^{1}H NMR resonances of Hd on the five member ring, and the asymmetric CH_2 protons and the *C-H proton at the chiral center were only slightly affected with 0.01-0.02 ppm upfield shifts. It is apparent that the chemical shifts of host **1** do not show significant changes; only slight upfield shifts of 0.01 to 0.08 ppm were observed. The following structures illustrate the CICS values of guests L-Trp and L-Phe with host **1**:



L-Trp



L-Phe

Several points may be garnered from these results: (1) the Ha and Ha' side of L-Trp, which can be viewed as the "head" of this guest molecule, deeply penetrated the cavity of **1** and experienced the largest π-π influence; (2) the hydrophilic zwitterion end of L-Trp, which can be viewed as the "tail" of this molecule, was left outside the cavity in contact with H_2O; and (3) the cavity of **1** appears to be very shallow. These three points can be easily rationalized, since the "head" of has the highest π-electron density available, and is very hydrophobic. In aqueous solution, this hydrophobic end wants to interact with other hydrophobic groups, such as the cavity of **1**, to minimize the thermodynamically unfavorable interactions with H_2O molecules. On the other hand, the hydrophilic zwitterion "tail" of L-Trp would likely be hydrogen-bonded to the surrounding H_2O molecules, which are mostly outside of the cavity of **1**.

This type of interaction in H_2O is reminiscent of protein molecules in which the majority of the hydrophilic, polar amino acid residues are located on the surface of these biopolymers in contact with H_2O, while the hydrophobic residues are mainly buried in the interior of these polymers to interact with each other. Finally, the depth of the cavity of **1** can easily be observed from the CPK model (Figure 1), and this resulted in a significantly smaller upfield shift of Hb and Hc, which were not shielded as much as Ha and Ha' by the π-electron

density of **1**. The above description of the molecular recognition process of L-Trp with **1** was shown in the energy minimized, space-filling model of **1** and the docking of L-Trp (Figure 3).

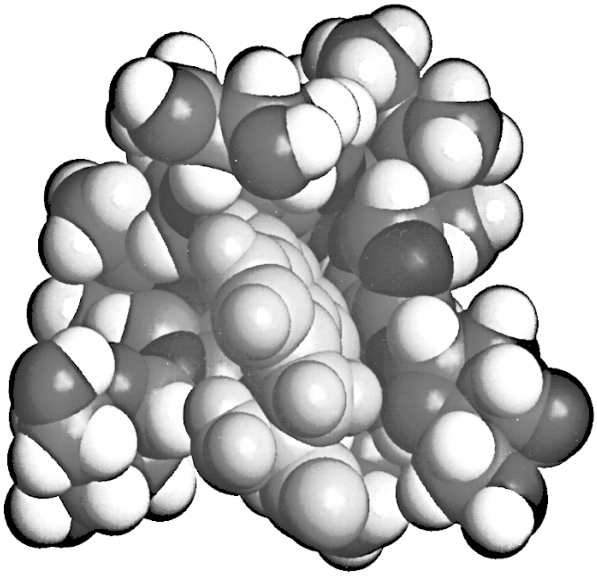


Figure 3: Computer docking of host **1** with L-Trp.

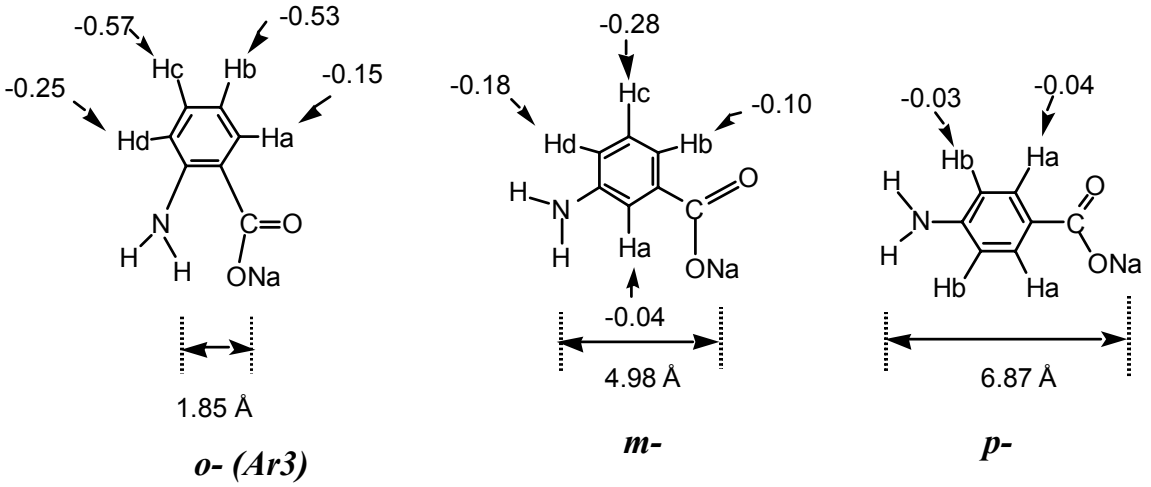
These overall results suggest that the molecular recognition of L-Trp with **1** can be described in a way that places the L-Trp aromatic rings inside of the host cavity with the aromatic plane, or more specifically, the line which bisects the C-H(a) and C-H(a') bonds parallel to the C3 axis of host **1**.

The association constants (K_a) for the host-guest complexation were estimated by using a standard NMR method[4a,b,8] to confirm the trends which were observed. The estimated K_a values, a value that encompasses the diastereomers of **1**, are in the range of 500-1000 M^{-1}, while free energies of host-guest complexation, ΔG^o values are in the range of –4 to –6 kcal/mol. It is noteworthy to mention that L-Trp, with its optimized steric orientation, electron donating N atom, and hydrophobic effects, has similar K_a and ΔG^o values with host **1** compared to similar interactions with L-Phe.[4b]

The host-guest molecular recognition process was also further substantiated by an intermolecular NOE study between **1** and L-Trp. In that study, the line broadening parameter was set to 4 Hz to minimize the subtraction error. When H8 of **1** was irradiated, weak negative intermolecular NOE signals of L-Trp's Ha, Ha', Hb, and Hc aromatic protons were observed. It is important to note that no intermolecular NOE signal was found between **1** and the solvent, D_2O, which excludes the possibility that the NOE data was an artifact. The moderate association constant (K_a = 607) for **1** and L-Trp, in comparison to the range of literature reported values[2a,2i,3b] of 10 to 10^6 M^{-1}, was thought to be partially responsible for the somewhat weak intermolecular NOE signals that were observed. Negative intramolecular NOE signals of **1**'s H1', H2, H2', H2", H3', and H4' protons were also observed when H8 was irradiated, and the intensities of these intramolecular NOE signals vary according to the distances between H8 and these protons. Similar results were seen when H2 of **1** was irradiated.

Molecular Recognition of Substituted Aromatic Carboxylic Acids.

Three substituted aromatic carboxylic acids, *o*-, *m*-, and *p*-aminobenzoic acids were selected as guests to extend the scope of our molecular recognition studies by interaction with host **1**. All three guests, *o*-, *m*-, and *p*-aminobenzoic acids, have the same functional groups, i.e., an electron-donating NH_2 group and an electron-withdrawing COO^- group; however, the two groups are separated from each other at different distances (positional isomers). At pH 7, the anionic forms of *o*-, *m*-, and *p*-aminobenzoic acids are the predominant species in concert with their pK_a values.[4a,b] The CICS values of these three guests by host **1** are presented in the following manner, with the upfield shifts denoted on the structures, and the distances between the NH_2 and the COO^- groups designated in angstroms:

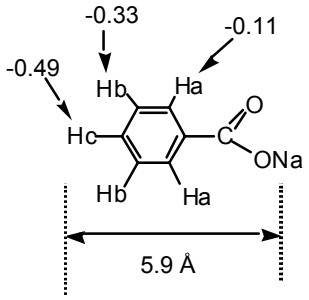


o- (Ar3) ***m-*** ***p-***

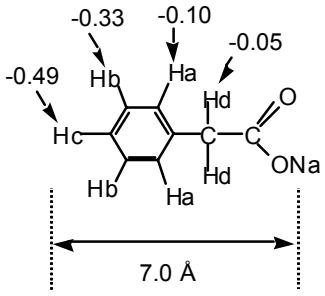
Interestingly, the minor substitution changes of these three positional isomers showed dramatically different CICS values and their interrelated K_a and ΔG^o values, by both π-π and hydrophobic interactions with **1**. The largest CICS values for *o*- (Hc) and *m*- (Hc) are 14 and 7 times larger, respectively, than that of *p*- (Ha). This observation can be explained by the steric effects of the guests, since the two hydrophilic functional groups which form H-bonds with the bulk H_2O need to avoid unfavorable interactions with the hydrophobic cavity of **1**. Moreover, these H-bonds with the bulk H_2O determine the orientations of *o*-, *m*-, and *p*-aminobenzoic acids as they approach host **1**; the hydrophobic end of guests *o*-, *m*-, and *p*-aminobenzoic acids must enter **1** more favorably. Therefore, guests with the most exposed hydrophobic portions, such as *Ar3*, should have the largest CICS values, as was observed. Molecular modeling studies confirm that the distances between the amino H atom and carboxylate O atom for *o*-, *m*-, and *p*-aminobenzoic acids are 1.85 Å, 4.98 Å, and 6.87 Å, respectively. With the increasing distances between these the two hydrophilic functional groups, from *o*-, *m*-, to *p*-aminobenzoic acids the steric hindrance also dramatically increases and, at the same time, the exposed hydrophobic portions decrease.

Molecular Recognition of Aromatic and Aliphatic Carboxylic Acids.

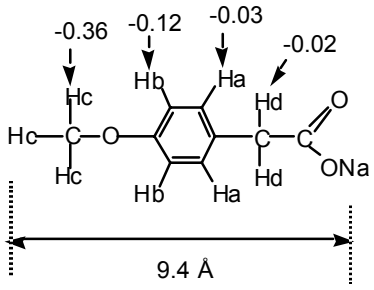
Three aromatic carboxylic acids, benzoic acid (Ar1), phenylacetic acid (Ar2), and 4-methoxyphenylacetic acid were selected as guests to probe the depth of penetration in host **1**, and, as well, two aliphatic carboxylic acid guests, cyclohexylacetic acid (Al1), and 1-adamantanecarboxylic acid (Al2), were also used to further study the importance of hydrophobic effects in the molecular recognition process with host **1**. According to their pK_a values, all of these carboxylic acids existed in the anionic form at pH 7.[4a,b] The CICS values of the three guests, Ar1, Ar2, and 4-methoxyphenylacetic acid, by host **1** are presented in a similar fashion as described above for the substituted aromatic carboxylic acids:



Ar1



Ar2



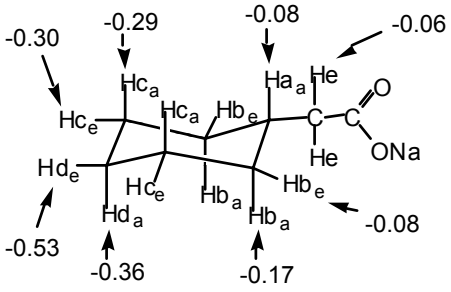
***p*-methoxyphenylacetic acid**

It is apparent that the CICS values for Ar1 and Ar2 are almost identical, indicating that one more CH_2 group between the benzene ring and the carboxylate has very little or no influence on the π-π/hydrophobic recognition process; the CH_2 group is close to the hydrophilic group of the guest, and therefore, was not intimately involved in the molecular recognition process. The CICS values for *p*-methoxyphenylacetic acid, which has a CH_3O group on the 4-position, are quite different from those for Ar1 and Ar2. The CICS values for *p*-methoxyphenylacetic acid with **1** are -0.36, -0.12, -0.03, and -0.02 ppm for Hc (methyl), Hb

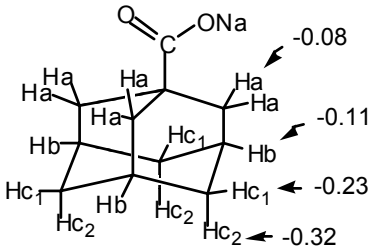
(aromatic), Ha (aromatic), and the Hd (CH_2) protons, respectively. The small CICS values for aromatic protons of *p*-methoxyphenylacetic acid suggest that the hydrophobic interaction is the major recognition effect, while π-π stacking is the minor contributor in this molecular recognition example. This result also suggests that the cavity of host **1** is shallow, which agrees well with the estimated cavity depth of ~ 4 Å.

Although the structure of guest Ar2 is very similar to that of L-Phe, their CICS values with **1** are quite different. This difference may be explained by inspecting the hydrophilic end of both guests. Guest L-Phe has two hydrophilic functional groups, NH_3^+, and COO^-, while Ar2 only has only one, and therefore, the hydrophilic end of L-Phe forms stronger H-bonds with the bulk H_2O solution. The strong H-bonds between L-Phe and the surrounding H_2O should prevent L-Phe from entering the cavity of **1** too deeply; the desolvation energies appear to be higher in this case.

For aliphatic carboxylic acid guests, Al1 and Al2, the CICS values of the two guests with host **1** are shown as before:



Al1



Al2

Surprisingly, the CICS values for these two aliphatic guests, especially Al1, are comparable, and in some cases, even greater than certain aromatic carboxylic guests. These results are in sharp contrast to the CICS values of several aliphatic amino acids, such as L-Leu and L-Ile,

which have relatively long hydrophobic side chains, indicating that the conformation and the number of C atoms (hydrophobicity, solubility in H_2O) of the guest molecules are of significant importance in the molecular recognition process. The "chair" form of Al1 should be predominant during the host-guest interaction, since it should be locked in this conformation by the relatively large CH_2COO^- group, and this should be a less sterically demanding conformation than the alternative "boat" conformation. The molecular recognition process of Al1 with **1** (K_a = ~760 M^{-1}, ΔG^o = -3.9) is shown in the energy minimized space-filling model of **1** and the docking of Al1 (Figure 4).

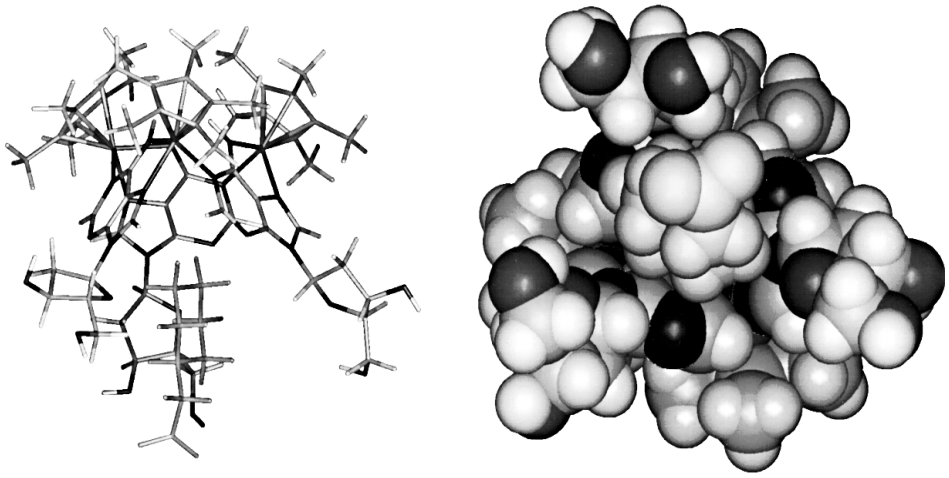


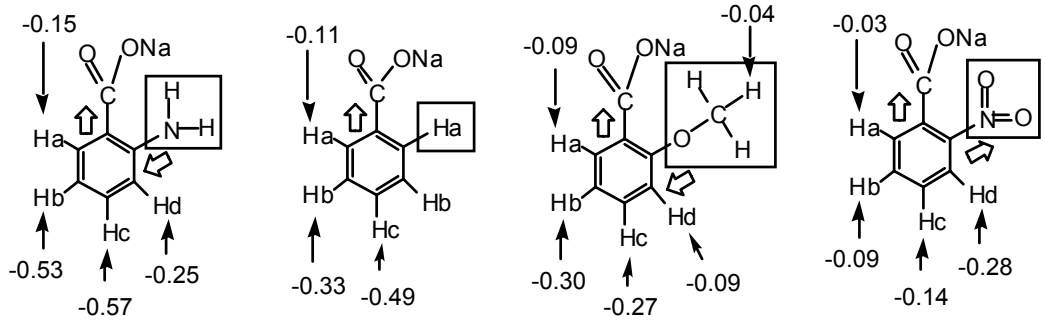
Figure 4. Computer docking experiment of host **1** with guest, cyclohexylacetic acid.

The bulky and rigid aliphatic carboxylate guest, Al2, also showed relatively large CICS values, which further strengthens the argument that conformational parameters and the hydrophobic effect of the guest molecules are important in the overall molecular recognition process. The interactions between Al2 and **1** (K_a = ~15, ΔG^o = -1.6; the $\Delta(\Delta G^o)$ between Al1 and Al2 with host **1** is ~ 2.3 kcal/mol) may be also due to the flexibility of the three 2'-

deoxyribose groups, which can possibly rotate away to make room for the bulky Al2; overall the apparent steric effect of Al2 limits this process.

In order to further determine the relative importance of π-π and hydrophobic effects in the molecular recognition process, a competition study between aromatic guest Ar2, and its closely related aliphatic guest, Al1, was undertaken. During this study, the concentrations of both competitors were kept constant, while that of **1** increased from 0 to 1 equivalent. Two control experiments, which held constant the concentration of *one* guest while varying the concentration of **1**, were also performed. The results show similar plots for the control and the competitive experiments for Ar2 and/or Al1,*which suggest that the π-π and hydrophobic effects may be of similar importance in aqueous solution*.

Two other guest molecules, *o*-methoxybenzoic acid and *o*-nitrobenzoic acid, were selected to study the steric and electronic influences of the different functional groups at the 2 position of benzoic acid with host **1**. Their CICS values, together with those of Ar3 and Ar1, were shown in the following manner as before:



It is apparent that the electron-donating abilities of the four functional groups in the boxes (see above) follow the order of $NH_2 > OCH_3 > H > NO_2$, while the steric hindrance order is: $OCH_3 \sim NO_2 > NH_2 > H$. Favorable electronic and steric properties for Ar3 (K_a =

~810, ΔG^o = -4.0) provide the largest CICS values, and hence K_a and ΔG^o values, while the steric advantage of Ar1 (K_a = ~710, ΔG^o = -3.9; $\Delta(\Delta G^o)$ between Ar3 and Ar1 is ~ 0.1 kcal/mol) makes its CICS values larger than those of *o*-methoxybenzoic acid (K_a = ~15, ΔG^o = -1.6) , even though OCH_3 is more electron-donating than an H atom. Therefore, sterically less demanding and more electron rich aromatic guests should have the largest CICS values in the molecular recognition process.

Discussion of the Molecular Recognition Process with Host 1

The driving force for the novel molecular recognition process that we presented in this chapter for host **1** (Figure 1) and the designated guests (Chart 1) is directly related to the use of water as the solvent. As clearly pointed out by Breslow,[5a] water maximizes the hydrophobic effect and the desolvation energies dictate the extent of the host-guest complexation. Therefore, water will solvate the hydrophilic end of the guests, while the desolvated hydrophobic substitutent enters the host cavity and interact via non-covalent processes.

The unique structure of the cyclic trimer hosts, which can be modified by substitutents on the N9 position of the adenine nucleus, represents a supramolecular bowl shaped molecule with a cavity opening of ~ 7.5 Å that is sufficiently large enough to accomodate many guests. The adenine ligands form the inner shell of the bowl, with the rhodium atoms basically acting as an anchor for both the dome (Cp*) and for the inner shell (adenine). It is also apparent that the coordinatively saturated Rh atoms are spectators during the molecular recognition process and do not directly take part in any of the non-covalent host-guest interactions.

The electron deficient adenine inner shell, which forms intramolecular η^2 bonds to Cp*Rh via NH6 and N7 and an intermolecular η^1 bond to Rh via N1 of another adenine (a

self-assembly mechanism that provides a cationic Cp*Rh cyclic trimer complex), was able to interact more favorably with the aromatic guests that contained electron-donating groups, such as L-Trp, Ar3, and *o*-methoxybenzoic acid. This result seemed to dictate that π-π interactions predominated in the molecular recognition process. However, by judiciously modifying the N9 substituent with the 2-deoxyribose group, host **1**, one could maximize the host-guest process and show that aliphatic carboxylic acids, such as Al1, interacted as favorably with host **1** as did aromatic guests, L-Trp, Ar3, and *p*-methoxyphenylacetic acid. Moreover, competition experiments with Ar2 and Al1, for host **1**, verified the equal importance of both non-covalent π-π and hydrophobic effects in the overall molecular recognition process.

Fish et al. also studied two other parameters, along with the above-mentioned electronic effect that appeared to affect the host-guest, molecular recognition process; namely, steric and conformational aspects. The importance of the steric effect can be seen with guests, *o*-, *m*-, and *p*-aminobenzoic acid, upon interaction with host **1**. As the positional isomers of aminobenzoic acids are changed from the ortho, to the meta, and then para positons, the extent of the host-guest interaction is dramatically decreased. The conformational effect is seen with a comparison of the aliphatic amino acid guests, such as L-Leu and L-Ile, that appeared not to interact with the host **1**, and guests Al1 and Al2, that were able to readily interact with the host **1**. Moreover, the solvophobic effects cannot be minimized, since the aliphatic amino acids are more soluble in water and, as well, their Hansch partition coefficients, log Poctanol, show them to have greater solubility in water than octanol.[5b]

It appears that conformationally rigid guests, as epitomized by Al1 and Al2, were better able to interact with host **1**, presumably by a hydrophobic effect, although the apparent steric effect of Al2 somewhat limits this molecular recognition process. In contrast, the aliphatic

amino acids, L-Leu, L-Ile, L-glycine, valine, alanine, and proline, suffer from conformational flexibility and, more importantly, their increased solubility in water, compared to L-Trp and L-Phe, significantly limits host-guest complexation. To reiterate, the electronic effect with electron-donating substituents, eg, -NH_2 and N-heterocyclic rings, enhanced the host-guest interaction, as shown by guests, Ar3 and L-Trp, while a guest with an electron-withdrawing substituent, guest o-nitrobenzoic acid with a o-NO_2 group on a benzoic acid nucleus, appears to have a more complicated host-guest interaction. Interestingly, the proton ortho to the NO_2 group in o-nitrobenzoic acid is upfield shifted to as great of an extent as that ortho proton in guest Ar3 containing an electron-donating o-NH_2 group. Apparently, the o-NO_2 group positions itself in proximity to the host cavity opening via a possible non-covalent H-bonding effect with the 2'-deoxyribose group, but this reasoning is speculative as of now.

In contrast, guest o-methoxybenzoic acid with an o-CH_3O- group, that has the largest steric demand of the ortho substituted benzoic acid, appears to position itself quite differently, since the ortho proton is slightly affected by the host-guest interaction. This latter discussion clearly shows that the extent of these host-guest interactions are a consequence of subtle changes of a multiple of parameters that are far more complicated than our current understanding.

Conclusions for Host 1 Non-covalent Interactions with Various Guests

The Fish group found that novel, bioorganometallic, supramolecular host, **1**, can readily recognize biologically important guests by a variety of non-covalent processes. The complexity of the interplay between these non-covalent processes; namely, π-π, hydrophobic, and subtle H-bonding effects, with further parameters of steric, electronic, conformational effects, and the ever present solvophobic effect in H_2O, clearly provides a driving force for

future studies with these unique hosts. For example, we have been able to use host **1** to recognize certain protein sequences (Chart 1, Dp TP)[4b] with terminal amino acids that favorably interact via the non-covalent processes we have attempted to elucidate in this chapter. Thus, conformational information that relates protein structure via the interaction of a supramolecular, bioorganometallic host is an exciting field that should be pursued further by organometallic chemists interested in this area of research.

A New Host, trans-[Cp*Rhη^{1}-(N3)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$, 2, for MolecularRecognition Studies with Aromatic Amino Acids: H-bonding as the Critical Recognition Parameter.

In the previous sections of this chapter, the molecular recognition process that involved; namely, π-π, hydrophobic, and possible subtle H-bonding effects, was described. Therefore, we wish to discuss a new molecular recognition process based primarily on selective hydrogen bonding interactions between the host, *trans*-[Cp*Rh–η^{1}-(N3)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$, **2**, and several examples of aromatic amino acid guests, L-tryptophan and L-phenylalanine, L-Trp and L-Phe, in water at pH 7.0. The X-ray structure of host **2** (Figure 5),[7,8] clearly shows the unique intramolecular H-bonding aspects of the ligand, 1-methylcytosine, with the Rh$_2$(μ-OH)$_2$ center. Thus, the μ-OH groups act as both H-donor and acceptor with the 2-carbonyl (OH--O=C,1.96 (1) Å) and NH$_2$ groups (HO--HNH,1.93 (1) Å), respectively.

Moreover, it was thought that an intermolecular recognition process also based on H-bonding to the μ-OH groups and the cytosine NH$_2$ and C=O functionalities might be feasible with the aromatic amino acid NH$_3$+ and COO- groups, without seriously disrupting the intramolecular hydrogen bonding regime shown in Figure 5.

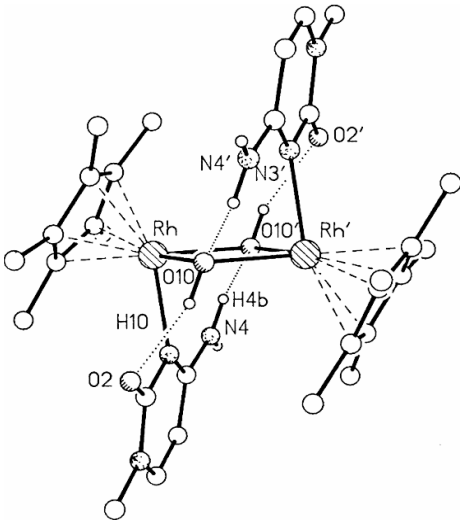
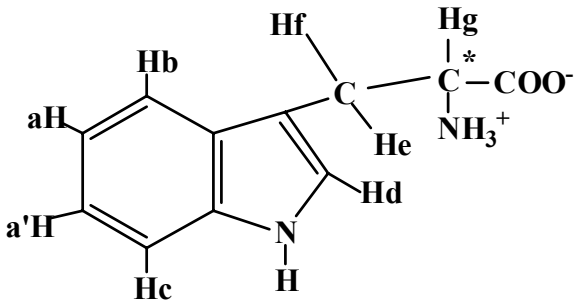


Figure 5: X-ray structure of host **2**.[7]

We again utilized 1H NMR techniques to discern the complexation-induced 1H NMR chemical shifts (CICS) for the host and the guests.[8] Table 1 shows the results with guest L-tryptophan (L-Trp) in the presence of host **2**. What is dramatically evident for L-Trp is the CICS values for $H_d(\Delta\delta = -0.34)$; $H_e(\Delta\delta = -0.15)$; $H_f(\Delta\delta = -0.07)$; and $H_g(\Delta\delta = -0.12)$, which were diametrically opposite to the previously reported Cp*Rh-2'-deoxyadenosine cyclic trimer molecular recognition studies with host **1**, where no upfield CICS for these designated protons were observed; in that process, the indole phenyl group was found inside the hydrophobic receptor, while the hydrophillic aromatic amino acid NH_3+ and COO- groups were outside in the water media, and the chiral C-H attached to these groups, as well as the adjacent asymmetric CH_2, were not affected by the magnetic anisotropy of the inner shell of the host adenosine ligands.

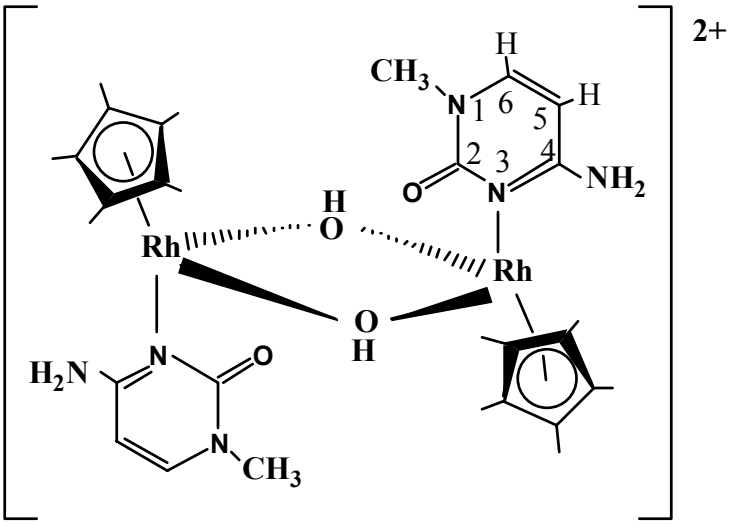
Table 1 CICS Shifts upon Host-Guest Recognition[a]



Free Tryptophan (δ)	With Host 2 (δ)	△δ
a 7.13	7.02	-0.11
a' 7.05	6.89	-0.16
b 7.58	7.16	-0.42
c 7.39	7.14	-0.25
d 7.16	6.82	-0.34
e 3.15	3.00	-0.15
f 3.34	3.26	-0.07
g 3.90	3.77	-0.12

[a] ^{1}H NMR shifts at pH 7.0, 300MHz, 1:1 host/guest ratio

Table 2. Host 2 ^{1}H NMR Data with Guests L-Trp and L-Phe[a]



2

Free Host 2(δ)		Guest L-Trp (δ)			Guest L-Phe (δ)			
		△δ		△δ		△δ		△δ
N-CH_3 3.24	2.83	-0.41	3.22	-0.02	3.23	-0.01	3.13	-0.11
H_6 7.44	7.26	-0.18	7.41	-0.03	7.42	-0.02	7.35	-0.09
H_5 5.83	5.52	-0.31	5.81	-0.02	5.81	-0.02	5.82	-0.01
Cp* 1.46	1.35	-0.12	1.35	-0.12	1.40	-0.06	1.40	-0.06

[a] ^{1}H NMR shifts at pH 7.0, 300MHz, 1:1 host/guest ratio

More importantly, two sets of signals for the host ligand, 1-methylcytosine, bound to Cp*Rh; the N-CH_3, H_5, and H_6 protons, were also observed. The CICS for one of the now apparently asymmetrical 1-methylcytosine ligands (Table 2) was similar to complex **2** alone, while the other had CICS upfield shifts for the N-CH_3 ($\Delta\delta$ = -0.41); H_5 ($\Delta\delta$= -0.31); and H_6 ($\Delta\delta$ = -0.18). Clearly, the CICS for one of the 1-methylcytosine ligands were affected by the non-covalent interactions with the indole ring of L-Trp and vice-versa. Thus, it appears plausible that the primary host-guest interaction of **2** with L-Trp was from a H-bonding process of the NH_3^+ and COO^- groups with **2**, enhancing non-covalent interactions of the 1-methylcytosine ligand with L-Trp.

In order to better understand these H-bonding and non-covalent interactions between host and guest, the Fish group conducted computer docking experiments to provide the energy minimized, space-filling/ball and stick model of **2** with a ball and stick model of guest L-Trp, as shown in Figure 6. The top view in Figure 6 demonstrates the H-bonding of the NH_3^+ group to one μ-O and to the C=O group of one of the 1-methylcytosine ligands, while the COO^- group H-bonds to a NH_2 group of the 1-methylcytosine ligand. This H-bonding scheme of **2** with L-Trp then provides that the remaining structure of the guest is fixed in relation to the host, as shown in the top and middle views of Figure 6.

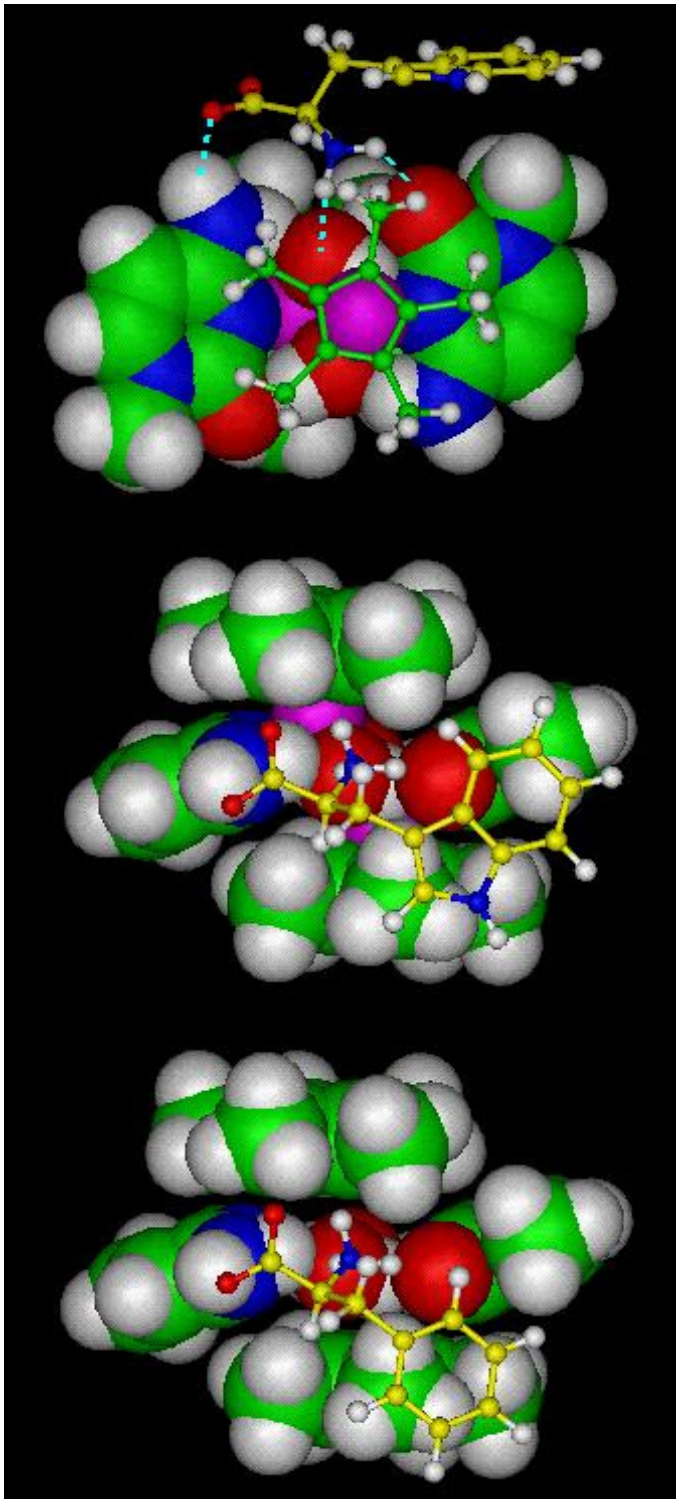


Figure 6: The top view of **2˙L-Trp**: H-bonding of the NH_3^+ group to one μ-OH and to the C=O group of one of the 1-methylcytosine ligands, while the COO^- group H-bonds to a NH_2 group of the other 1-methylcytosine ligand. Middle View of 2.L-Trp: Bottom View of 2.L-Phe. N (blue); O (red); H (white) Rh (magenta).

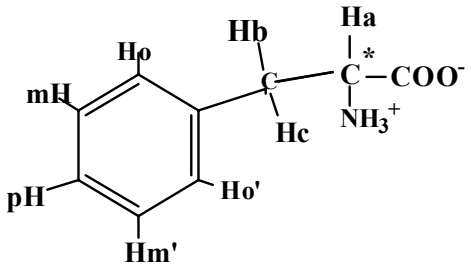
Therefore, the indole group is positioned orthogonal to the plane of the 1-methylcytosine ligands in host **2**, while selectively effecting one of the two 1-methlycytosine groups, accounting for this ligand's asymmetry, and the upfield shifts observed in the NMR CICS values (Table 1). Figure 6 also shows the plausible reason that H_b was appreciably shifted upfield due to its proximity (middle view) to the C=O group of 1-methylcytosine, while also noting the asymmetric CH_2 hydrogens, where H_e is more affected by the CICS effects then H_f (Table 1). It is also interesting to note the appreciable upfield shift for H_d ($\Delta\delta$ = - 0.34), which is shown in Figure 6, middle, and we attribute this to the proximity to one of the Cp* ligands via a plausible CH-π non-covalent interaction. Moreover, the potentially asymmetric Cp*Rh groups are co-incident in the NMR (only one signal),even though the nitrogen ring of the indole nucleus appears (Figure 6, middle) in the docking experiment to be somewhat orthogonal to one of the Cp* ligands.

Fish and co-workers then studied guest , L-phenylalanine (L-Phe), with host **2** (Table 3), and found a striking difference in the CICS for the 1-methylcytosine ligands, as opposed to that with guest **2**, L-tryptophan. Relatively, smaller CICS values were observed for the 1-methylcytosine ligands in the presence of L-Phe; for example, one of the 1-methylcytosine ligands was not greatly effected by the host-guest interaction and showed the N-CH_3, H_5, and H_6 protons with average upfield shift values of $\Delta\delta$ = ~0.017 for the non-covalent interactions (Table 2). The other 1-methylcytosine ligand had N-CH_3, H_5, and H_6 proton upfield shifts of $\Delta\delta$ = -0.11, -0.01, and –0.09, respectively.

Figure 6 (bottom) shows the docking experiment results with **2** and L-Phe, and clearly a similar H-bonding process of the NH_3^+ group to one of the oxygen atoms of the Rh(μ-OH) assembly, and the C=O group of one of the 1-methylcytosine ligands, while that of the COO^-

group to a NH_2 group, was deemed appropriate from the energy minimized structure found in Figure 6, Top. The critical aspect about this host-guest interaction is that, in analogy to the nitrogen ring proton, H_d, in L-tryptophan, the H_p, H_m, and H_o protons at 7.273, 7.271, and 7.19 δ were upfield shifted, Δδ = -0.28, -0.36 and -0.35, respectively (Table 3). Clearly, the aromatic protons of guest L-Phe were upfield shifted by the proximity to both the C=O of one of the 1-methylcytosine ligands, and one of the Cp* ligands. It is also important to notice that the asymmetric CH_2 protons are also substantially shifted upfield with values of Δδ = -0.29 and –0.42, respectively. We also observe only one Cp* signal that was shifted upfield with Δδ =-0.06, as was the case with the host-guest complex of **2** with L-Trp.

Table 3 CICS Shifts upon Host -Guest Recognition [a]



Free L-phenylalanine(δ)	Interaction with Host 2 (δ)	△δ
a 3.85	3.79	-0.07
b 2.98	2.69	-0.29
c 3.15	2.73	-0.42
o,o' 7.19	6.84	-0.35
m,m' 7.271	6.91	-0.36
p 7.273	7.00	-0.28

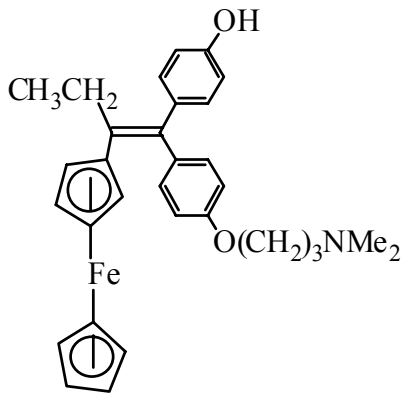
[a] ^{1}H NMR shifts at pH 7.0, 300MHz, 1:1 host/guest ratio

Conclusions on Molecular Recognition with Host 2

In this section, a new bioorganometallic recognition process with host **2** and several examples of aromatic amino acid guests was demonstrated that depends on selective H-bonding of the NH_3^+ and COO^- groups of the aromatic amino acids, L-Trp and L-Phe, to an oxygen of one of the Rh(μ-OH) assemblies, and C=O and NH_2 groups of the Rh bound 1-methylcytosine ligands, in water at pH 7.0 . The significance of this new, highly selective, host-guest process is that it can be thought of as a model for H-bonding of biologically significant guests to metalloenzymes and DNA/RNA.[1a,4a,b]

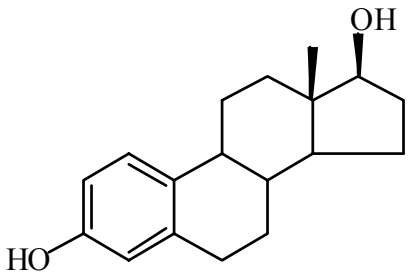
Computer Docking Experiments of Organometallic Pharmaceuticals at Estrogen Receptor Binding Sites: Selective, Non-Covalent Interactions with Hormone Proteins

Recently, Jaouen and co-workers discovered that an organometallic derivative of the known breast cancer drug, Tamoxifen (Hydroxtamoxifen, a liver metabolite, is the active drug), Ferrocifen, **3**, and its derivatives, were potential candidates for breast cancer therapy, as well as other cancers.[4g,9] This seminal finding has created a new paradigm; namely, the field of organometallic pharmaceuticals.[9,10] Since the X-ray structure of the estrogen hormone receptor site (ERα) has been accomplished, which is thought to be the major receptor protein implicated in hormone-dependant breast cancers, therefore, it was appropriate, utilizing computer docking/energy minimization experiments at the receptor site, to discern the conformation and non-covalent interactions of Ferrocifen, **3**, and other organometallic drug derivatives, with the surrounding simplified protein structure.[4g,9,10]



3

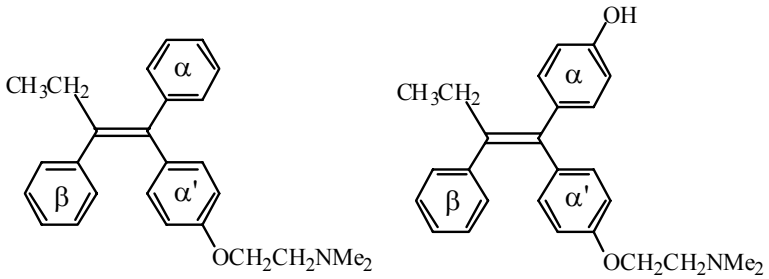
Moreover, the identification of novel targets of estrogen action provides an increasing degree of complexity to the understanding of mechanisms by which this hormone elicits many of its normal, as well as pathological effects. Estradiol, **4**, the archetype of estrogens, has been implicated in a number of problems from fertility questions to several types of cancer, including frequent diseases, such as osteoporosis, cardiovascular, and metabolic disorders. It is well known that the effect of estradiol is mediated through its ability to bind to the estrogen hormone receptor site.



Estradiol, **4**

A molecular view of the binding modes existing both with an agonist (**4**) as well as an antagonist; (Tamoxifen, 4-hydroxytamoxifen, blocks estradiol from the receptor site) with similar nanometer distances, based upon these X-ray determinations, can now be utilized to examine the consequences of the attachment of an organometallic moiety, for example,

compound **3**, to a modified drug structure; i. e., hydroxytamoxifen modified to **3** (*note the optimized bioactivity for **3** was for a three spacer methylene group on the ether oxygen*), with respect to the receptor binding site. Since we have two groups of organometallic drug derivatives based on an estrogenic, complex **5**, or an anti-estrogenic, complex **3**, structural effect, then we will illustrate the different non-covalent binding regimes with an example of each type of behavior.



Tamoxifen 4-Hydroxytamoxifen (Z)

Figures 7 defines the anti-estrogenic, organometallic complex, **3**, as to its conformation in computer docking/energy minimization experiments with the estrogen receptor site proteins, and demonstrates important non-covalent interactions with the amino acids depicted in the Figure. Thus, several hydrogen bonding regimes are discernable, for example, between aspartic acid carboxylate 351 (1.868 Å) and one of the N-CH_3 groups of the ether side chain, $O(CH_2)_3N(CH_3)_2$, the carboxylate of glutamic acid 353 and the phenolic hydrogen (1.577 Å), and the arginine 394 NH with the phenolic oxygen (2.061 Å). Moreover, one of the Cp ligands of the ferrocene group has a non-covalent CH-π interaction with the histidine 524 imidazole ring.

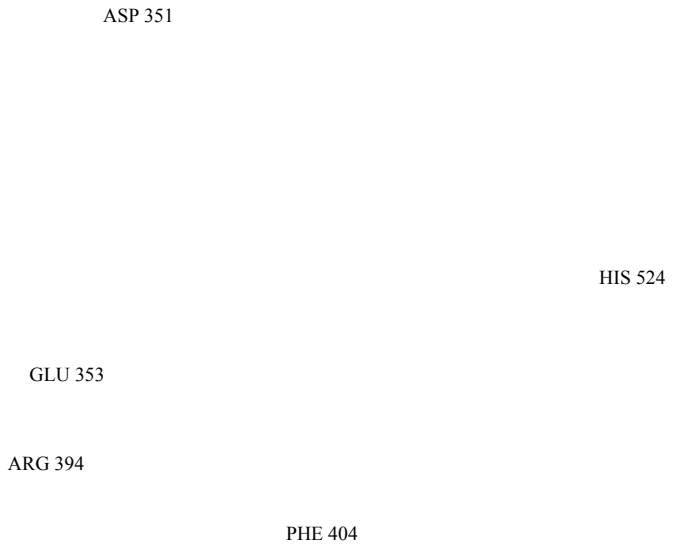


Figure 7: Ferrocifen derivative (Z isomer), **3** , docked at the estrogen protein receptor site and shows the organometallic complex inside the antagonist binding site of the estrogen receptor.

In contrast to the anti-estrogenic, **3**, (Z isomer), binding mode to the estrogen protein receptor site, the ligand binding domain for estrogenic **5** was similar to estradiol, **4**, with the exception of the ruthenocene Cp ligand, attached to a rigid acetylenic linkage. Clearly, Figure 8 shows the dramatic conformational and non-covalent bonding differences with the estrogen protein binding site between the two organometallic modified drugs, **3** and **5**. Significantly, one of the Cp rings of the ruthenocene group is now in a non-covalent π-π interaction (3.211Å), with the histidine 524 imidazole group, while the imidazole ring NH group is hydrogen bonding(2.722 Å), to the 17 α OH group. Other pertinent hydrogen bonds are with the A ring phenolic OH with both the glutamic acid carboxylate 353 (2.722 Å), and the arginine 394 NH (3.101Å).

Figure 8. 17α–ruthenocenylethynylestradiol, **5**, docked at the estrogen protein receptor site. The ethynyruthenocenyl group is also bordered in its lower side by two hydrophobic amino acid residues Met 343 and Met 421. A shrinkage, which is well adapted to accommodate the rigid ethynyl group, can be clearly seen in front of the 17α-position of the hormone. This allows the ruthenocenyl group to avoid steric constraints inside the cavity.

Therefore, the exciting finding of possibly why organometallic pharmaceutial, **3**, is a potential anti-cancer agent from bioassay results, while the organometallic modified estradiol, **5**, is not, could be related to the conformational changes in the estrogen receptor protein upon binding of the drug. This can be depicted in the more complex receptor protein site with **3**, Figure 9, where the apparent steric effects of the $O(CH_2)_3N(CH_3)_2$ side-chain appears to cause Helix 4 and Helix 12 to leave a gap between them. This factor is opposite to that of complex **5**, where there is no gap (similar to a mouse trap) between Helix 4 and Helix 12, and this plausible reason, among others, may explain why **3** is a potential drug for breast cancer, and **5** is not. Another important aspect is the fact that **3**, with a ferrocenyl ligand can be readily oxidized to a ferrocenium ion, and in the process of degradation to Cp and Fe(III), can generate

an oxygen radical species that can provide the cytotoxic effect, by possibly reacting with DNA in proximity to the binding domain at the estrogen receptor site.[11]

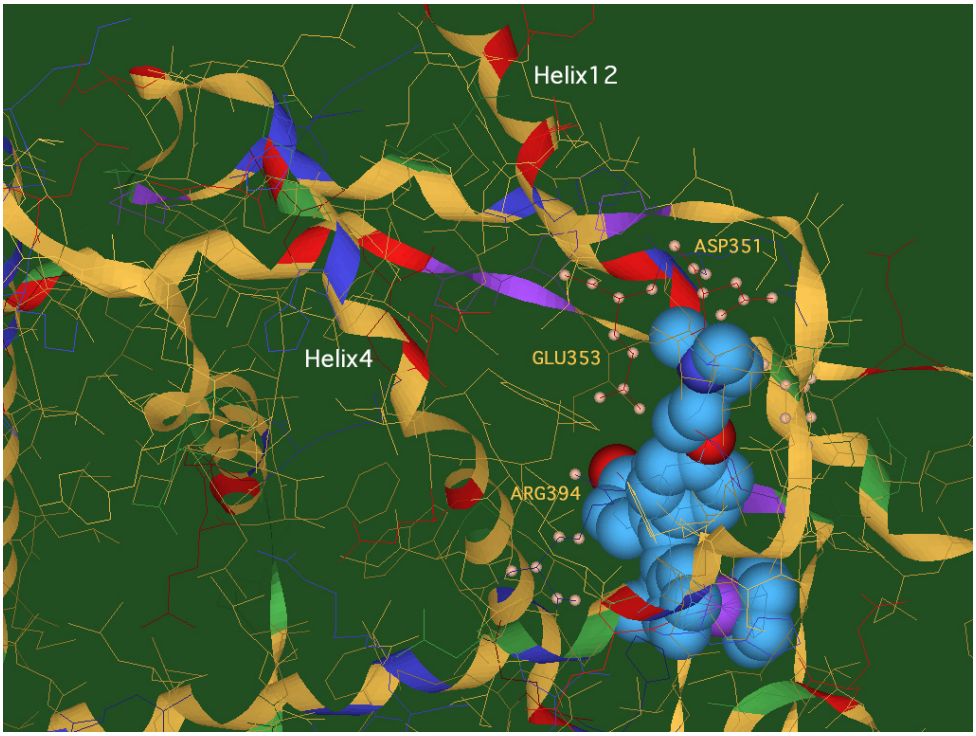
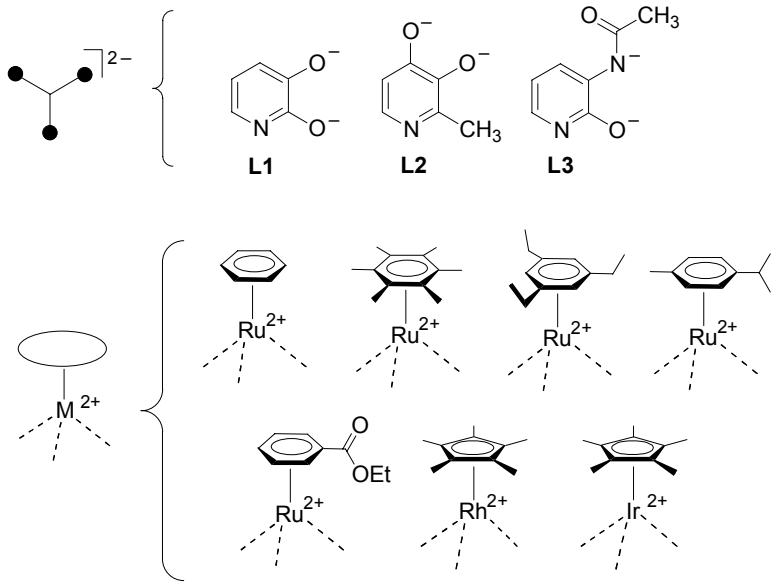


Figure 9: Ligand binding domain at the estrogen receptor site of potential organometallic pharmaceutical, **3**.

Organometallic Ionophores: Structure and Selectivity to Alkali Metal Ions

Taking a similar synthetic approach to the self assembled Cp*Rh cyclic trimer structures, such as **1**, that were used as hosts for biomolecules, Severin and co-workers have developed a novel, self-assembly approach to organometallic ionophores, biomolecular organometallamacrocycles that selectively sequester alkali metal ions.[6] Severin and co-workers have used this self-assembly approach to these synthetic targets for potential medical and analytical applications.[12] Scheme 1 demonstrates the versatility of both organic ligands and π-organometallic fragments as starting materials.



Scheme 1: Ligands, L1-L3, and organometallic fragments for the synthesis of potential organometallic ionophores.

The self-assembly process begins with the chloro-bridged complexes $[(\pi\text{-ligand})MCl_2]_2$ (M = Ru, Rh, Ir), which reacted with ligands L1-L3 in the presence of base. The 3-oxo-pyridonate ligand, L1, provided organometallamacrocyclic complexes of the general formula $[(\pi\text{-ligand})M(L1)]_3$ with various arene ligands; for example, C_6H_6, C_6Me_6, 1,3,5-$C_6H_3Et_3$, cymene, $C_6H_5CO_2Et$, and with Cp* ligands, (Figure 10). Trinuclear complexes are likewise formed with the bridging ligands L2 and L3 in combination with (cymene)Ru^{2+} (L2, L3) and Cp*Ir^{2+} fragments (L2) .

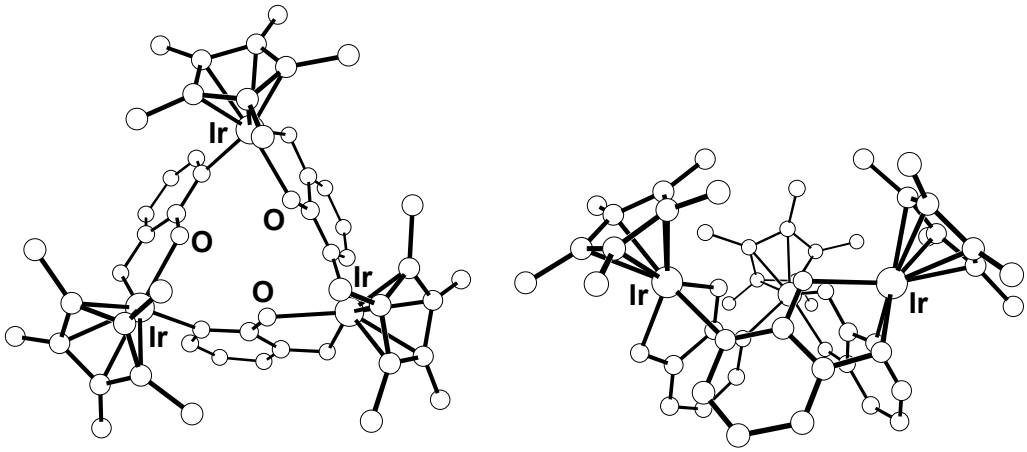


Figure 10. X-ray structure of $[Cp^*Ir(L1)]_3$. Left: view along the pseudo C_3 axis; Right: view from the side.

The tridentate ligand, L1, bridges the metals by coordination via the oxo groups and the pyridine nitrogen atom. The 12-membered organometallamacrocycles contain three oxygen atoms positioned in close proximity to each other, and can thus be regarded as organometallic analogues of 12-crown-3.

Similar to what was found for L1, complexes with L2 show a (pseudo) C_3 symmetric geometry with three tetrahedral (cymene)Ru or Cp*Ir corners (Fig. 11). Again, the ligand was coordinated via the oxygen atoms and the ring nitrogen atom to the metal atoms. The planes defined by the heterocyclic ligand; however, are almost perpendicular to the plane defined by the metal atoms, resulting in an expanded macrocycle with M·M distances of 7.24 Å.

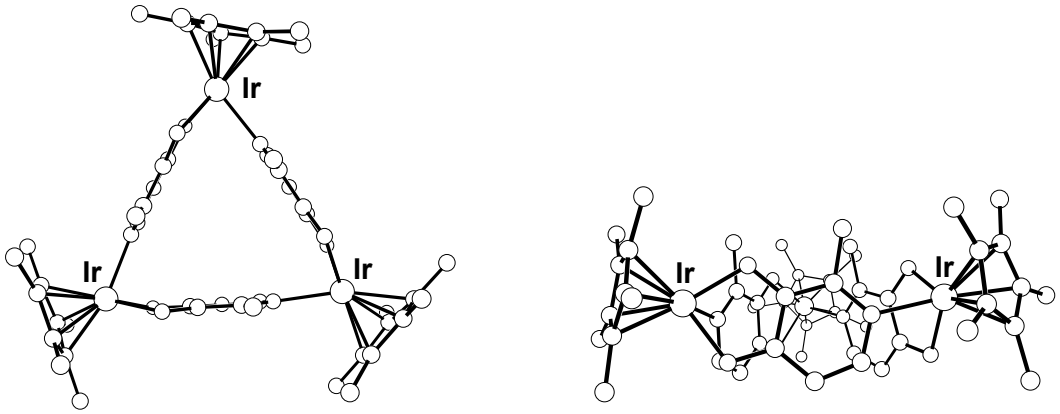
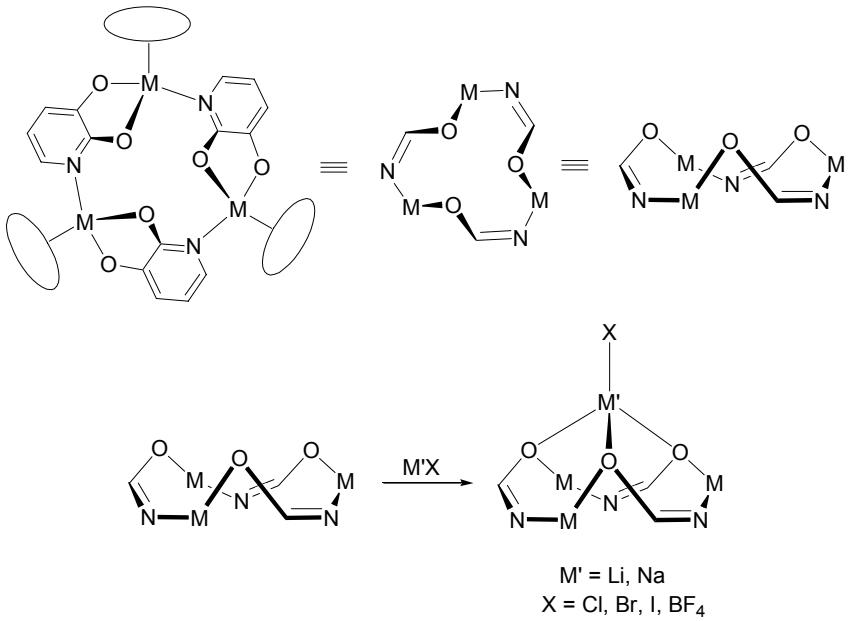


Figure 11. X-ray structure of $[Cp^*Ir(L2)]_3$. Left: view along the C_3 axis; Right: view from the side.

The compounds $[(\pi\text{-ligand})M(L1)]_3$ represent the first *organometallic crown complexes* to be synthesized.[6] Similar to their organic counterparts, organometallacrown complexes are able to bind cationic guests such as alkali metal ions. Thus far, Severin and co-workers have been able to isolate and structurally characterize adducts of $[(\pi\text{-ligand})M(L1)]_3$ with LiCl, $LiBF_4$, LiF, LiFHF, NaCl, NaBr and NaI.[12] In all cases studied, the metal ion M' was bound to the three adjacent oxygen atoms of the receptor. The fourth coordination site is generally occupied by the anion X (Scheme 2).



Scheme 2. Organometallic complexes of the general formula $[(\pi\text{-ligand})M(L1)]_3$ as receptors for lithium and sodium salts.

The coordination to guest molecules could be easily detected by ^{1}H NMR spectroscopy: upon binding to lithium or sodium salts, the signals for the pyridonate ligands, and the signals of the π-ligand, were shifted towards lower field (Figure 12). If the guest M'X was added in substoichiometric amounts, two sets of signals were observed, indicating that the exchange of M'X was slow on the NMR time scale. This makes the quantitation of adduct formation, under different conditions, very facile.

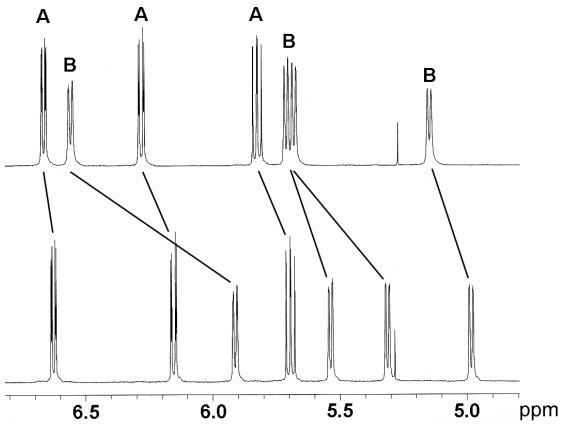


Figure 12. Aspects of the ^{1}H NMR spectrum ($CDCl_3$) of the receptor $[(cymene)Ru(L1)]_3$ (bottom) and the corresponding NaCl adduct (top). The signals of the cymene π-ligand are denoted with "B", the signals of the bridging pyridonate ligand L1 with "A".

The stabilities of the host-guest complexes are remarkably high. If the adduct $[(\pi\text{-ligand})M(L1)]_3$. M'X was dissolved in $CDCl_3$ (c = 10 mM), only the host-guest complex could be observed by ^1H NMR spectroscopy. The association constant must therefore be greater than 10^5 L mol^{-1}. To quantify the stability, we have performed competition experiments with various crown ethers and cryptands. The experiments have revealed that the association constants of the organometallamacrocyclic receptors $[(\pi\text{-ligand})M(L1)]_3$ are significantly greater than those of crown ethers, while being similar to those of macrobicyclic ionophores, such as 2.2.1-cryptand (for NaCl adducts) and 2.1.1-cryptand (for LiCl adducts).

As usual, lower values were found when using more polar solvents. When the NaX adducts were dissolved in CD_3OD, signals for the free and the complexed receptors $[(\pi\text{-ligand})M(L1)]_3$ could be observed by ^1H NMR spectroscopy. Thus, a direct calculation of K_a was then possible. For the halide salts, values between $K_a = 1.1 \pm 0.5\ 10^2$ L mol^{-1} (X = Cl, (□-ligand)M = (C_6H_6)Ru) and $K_a = 3.5 \pm 0.5\ 10^3$ L mol^{-1} (X = Cl, (π-ligand)M = (cymene)Ru) were obtained. Moreover, the stability of the Na^+ complexes depends on the nature of the anion. Thus, NaI adducts showed smaller K_a values than the NaCl adducts. The Li^+ adducts of the receptors $[(\pi\text{-ligand})M(L1)]_3$ generally displayed a greater stability then the corresponding Na^+ adducts; even in polar solvents, such as methanol, the host-guest complex was the only one that was detected by NMR with the $[(\pi\text{-ligand})M(L1)]_3$. LiCl complexes that indicated a K_a value of > 10^5 L mol^{-1}. The x-ray structure of the NaBr adduct with $[(\pi\text{-}C_6H_6)Ru(L1)]_3$ is shown in Figure 13.

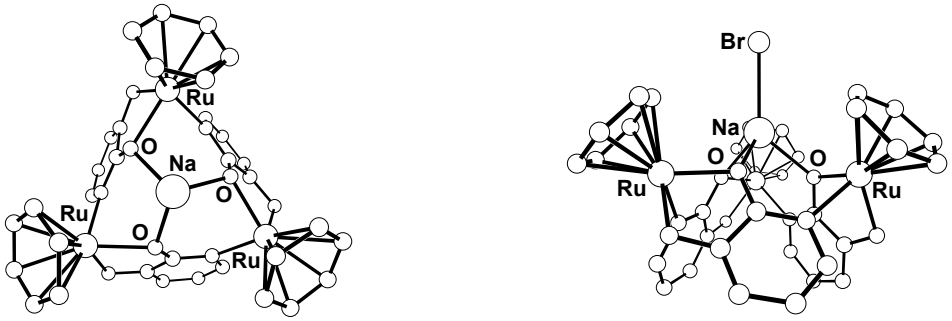
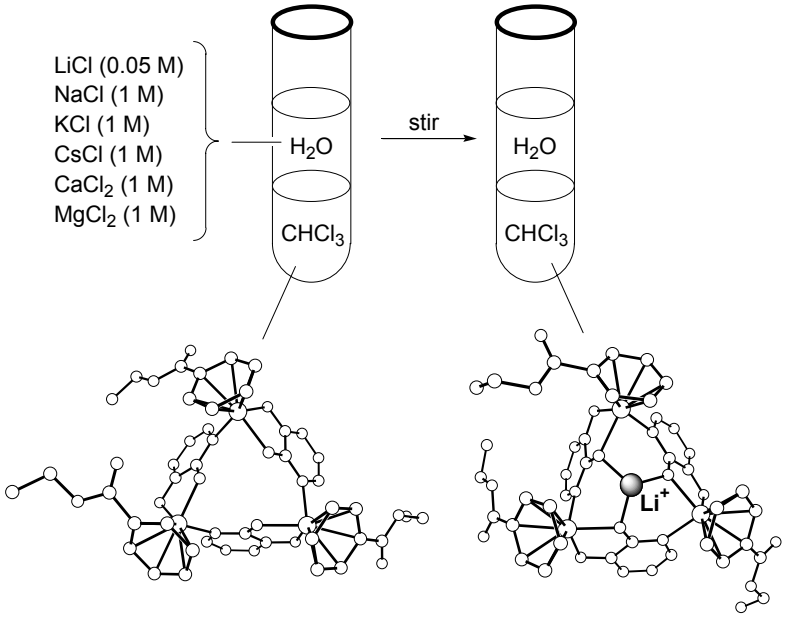


Figure 13. X-ray structure of the receptor $[(C_6H_6)Ru(L1)]_3$ with a NaBr guest molecule. Left: view along the pseudo C_3 axis, the bromine atom is not shown; Right: view from the side.

The surprisingly high stability of the LiX and NaX complexes could be attributed to several facts: a) The receptors are very rigid and clearly preorganized to bind lithium or sodium ions. When binding the guest molecules, the bond length and angles change only slightly. b) The salts are bound as an ion pair, which was energetically very favorable in organic solvents, such as chloroform. c) The energetic costs for the desolvation of the receptors was very low, since a maximum of one water molecule could fit inside the binding cavity.

The receptors $[(\pi\text{-ligand})M(L1)]_3$ not only showed a very high affinity for a certain alkali metal ion, but they also showed very high selectivity. The Li^+ adducts were formed with all receptors. The Na^+ adducts; however, were only formed with $(\pi\text{-ligand})M = (C_6H_6)Ru$, (cymene)Ru and $(C_6H_5CO_2Et)Ru$, while the K^+ adducts have not been observed at all. The pronounced selectivity can be explained by the geometry of the organometallacrown complexes; the π-ligands formed the walls of a rather rigid binding cavity. For small π-ligands, such as benzene, sodium ions were able to easily enter. Larger π-ligands, such as hexamethyl-benzene, efficiently block the binding site and Li^+ specific receptors were obtained.

The host-guest chemistry of the ruthenium complex $[(C_6H_5CO_2Et)Ru(L1)]_3$ proved to be of special interest. Although this receptor is principally able to bind Na^+ ions, it showed an outstanding affinity and selectivity for Li^+ salts.[12b] This was evidenced by the following experiments: An aqueous solution containing LiCl (50 mM), together with a large excess of NaCl, KCl, CsCl, $MgCl_2$ and $CaCl_2$ (1 M each), was reacted with a chloroform solution of this receptor, where the exclusive and quantitative extraction of LiCl was observed (Scheme 3). This was very remarkable for two reasons. Firstly, the extraction of LiCl from water was in principle very difficult to accomplish, due to the high enthalpy of hydration of Li^+ (– 521 kJ/mol) and Cl^- (– 363 kJ/mol). Secondly, the enthalpy of hydration of the other alkali metal ions is much smaller. Therefore, the exclusive formation of the LiCl adduct was indicative of extremely high selectivity for this alkali metal ion.



Scheme 3. Selective extraction of LiCl from an aqueous solution containing a large excess of alkali and earth alkaline metal salts using the receptor $[(C_6H_5CO_2Et)Ru(L1)]_3$.

As shown in Scheme 3, $[(C_6H_5CO_2Et)Ru(L1)]_3$ provides an organometallamacrocycle that is highly selective to Li^+ ions over the more highly concentrated Na^+ ions.[12] The CPK models of this organometallic ionophere, and that of the Li complex (Cl omitted for clarity) are shown in Figure 14.

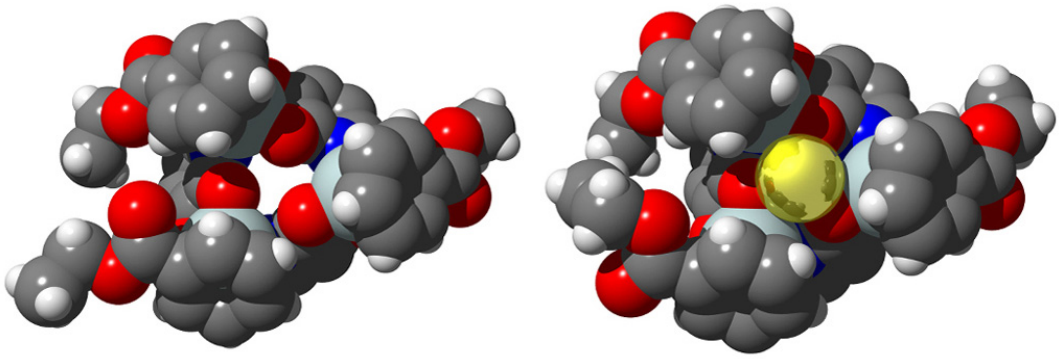


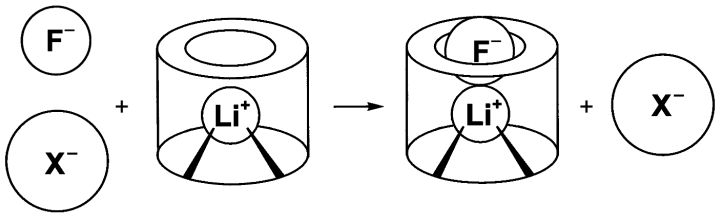
Figure 14: Left, Organometallic Ionophore, $[(C_6H_5CO_2Et)Ru(L1)]_3$, Right: Li complex.

In this context, it should be mentioned, that lithium salts such as Li_2CO_3 are among the most frequently used drugs for the treatment of manic depression. Due to its narrow therapeutic range, the Li^+ concentration in the blood of the patients needs to be controlled on a regular basis. Since blood has a relative high concentration of Na^+ , as compared to Li^+, the utilization of chemosensors has thus far have shown only very limited success. Thus, the use of these organometallamacrocycles, in conjunction with electrochemical techniques, for selective chemosensors, are presently being pursued by Severin and co-workers.[12c]

Specific Fluoride Receptors

Since the coordination of ion pairs to $[(\pi\text{-ligand})M(L1)]_3$ receptors was energetically very favorable, the possibility of utilizing complexes of this nature as specific fluoride receptors was investigated. The basic idea is schematically shown in Scheme 4. A lithium ion,

which serves as a binding site, is coordinated inside a [(π-ligand)M(L1)]$_3$ receptor. The accessibility of the Li^+ center is controlled by the steric requirements of the π-ligand. If large ligands were employed, only the small fluoride anion was able to enter the cavity, whereas larger anions were effectively blocked. Since the radius of the fluoride ion is significantly shorter than that of most other anions, a highly specific receptor was obtained.



Scheme 4. Schematic representation of a specific fluoride receptor based on a Li^+ containing organometallamacrocycle.

To understand this concept, the complex [Cp*Ir(L1)]$_3$ • $LiBF_4$ had appeared to be ideally suited as a highly specific receptor for a fluoride ion. NMR data showed that in solution ($CDCl_3/CD_3CN$, 2:1) the weekly bound BF_4^- ion was not found to be coordinated to the lithium ion. If Bu_4NF was added to this solution, signals of the ion-paired complex [Cp*Ir(L1)]$_3$• LiF were immediately observed by ^{19}F and ^7Li NMR spectroscopy. The LiF complex was even formed in the presence of a large excess of other anions X (X^- = Cl^-, Br^-, I^-, NO_3^-) indicative of a fluoride-X^- selectivity of higher than 10^3.

The CPK model of an x-ray structure of [Cp*Ir(L1)]$_3$ • LiF provides an explanation for this selectivity (Figure 15). The fluoride ion was found to be positioned at the opening of the cavity, closely surrounded by the three Cp* ligands. As a result, the four very short CH··F contacts between the Cp* ligands and F^- could be observed (CH···F = 2.15 – 2.28 Å). This

very tight encapsulation of the fluoride ion was expected to contribute to the overall stability of the host-guest complex and prevented the coordination of larger anions.

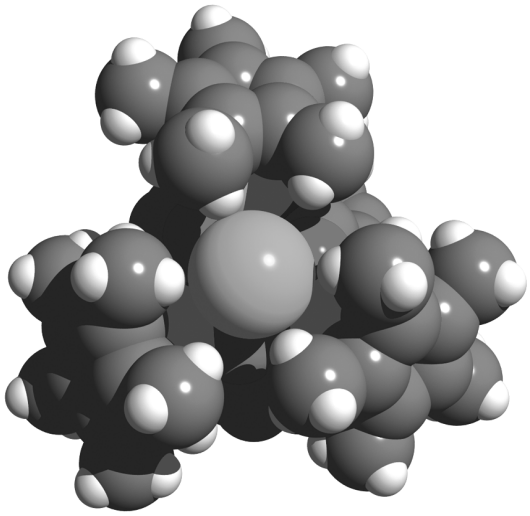


Figure 15. CPK model of the x-ray structure of $[Cp^*Ir(L1)]_3 \bullet LiF$ (view along the pseudo C_3 axis). The fluoride anion is tightly encapsulated by the Cp* ligands.

When a solution of the complex $[Cp^*Ir(L1)]_3 \bullet LiBF_4$ in $CHCl_3/CH_3CN$ (2:1) was analyzed by differential pulse voltammetry, the peak potential for the first oxidation can be observed at 890 (± 3) mV (against Ag/AgCl). Upon addition of five equivalents of F^- the complex is significantly easier to oxidize (ΔE = –203 mV). A possible explanation for this shift is the reduced electron withdrawing character of the ion-paired LiF guest compared to that of the solvated lithium ion. In agreement with the NMR studies, only small changes were observed upon addition of Cl^-, Br^-, NO_3^-, HSO_4^- or ClO_4^- salts (ΔE < 24 mV). Similar results were also obtained in solutions containing methanol. The complex $[Cp^*Ir(L1)]_3 \bullet LiBF_4$ was, therefore, a highly selective chemosensor, which allows the detection of fluoride anion by electrochemical means, even in protic solvents.[6]

Several other LiF and LiFHF complexes were also characterized by single crystal X-ray analysis (Figure 16). As expected, the lithium cation was coordinated to the three oxygen atoms of the receptors. The fourth coordination site was occupied either by the fluoride or the hydrogen difluoride anion. For the LiF complexes, the Li–F bond length was found to be between 1.77 and 1.81 Å. These values were found to amongst the smallest Li···F distances reported thus far, highlighting the unique situation of monomolecular LiF inside these organometallamacrocyclic hosts. For comparison, crystalline LiF has a Li···F distance of 2.009 Å. The difluoride anions were found to be coordinated in a bent fashion to the lithium ion (Li–F–F = 123 – 159 °). The F···F distances observed (2.25 – 2.30 Å were similar to what was found for crystals of hydrogen difluoride salts (2.24 – 2.28 Å).

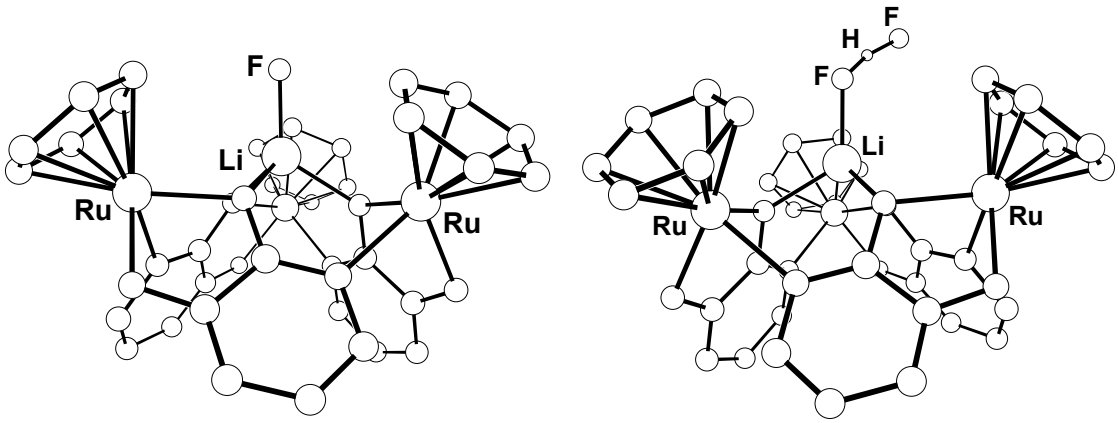


Figure 16. X-ray structures of the LiF (left) and the LiFHF (right) complexes utilizing receptor $[(cymene)Ru(L1)]_3$. Cymene side groups have been omitted for clarity.

Organometallic Ionophores Conclusions

There appears to be considerable interest in synthetic receptors with high affinity and selectivity for alkali metal ions. The current approaches towards this goal are often accompanied with substantial synthetic efforts that lacked self-assembly techniques. Severin and co-workers have synthesized new receptors for small cations and anions by self-assembly

of organometallamacrocyclic complexes.[6,12] Compared to other synthetic ionophores, the Severin et al. approach offers major advantages: a) These synthetic schemes could be accomplished in one step using simple starting materials. b) The presence of guest molecules could be detected electrochemically. c) Due to a very high degree of preorganization, excellent affinities and selectivities were observed.

The modular nature of these assemblies makes it very facile to incorporate many structural variations of these organometallamacrocyclic complexes. Given the exceptional performance of these organometallamacrocyclic receptors when compared to classical ionophores, such as crown ethers and cryptands, various applications can be envisioned in the future, including studies in water.[6,12e]

Molecular Recognition Chapter Conclusions

Molecular recognition studies with organometallic supramolecular hosts, having structures based on biological ligands; for example, DNA/RNA bases, and Cp*Rh groups, critical for the superstructure, were reviewed in their non-covalent, π-π, hydrophobic, and H-bonding interactions with various biological molecules, such as aromatic amino acids. Furthermore, self-assembled organometallamacrocyclic ionophores, which selectively bind alkali metal ions, such as Li^+ ions, represents potential new applications in mental health analytical methods.

Alternatively, it was also demonstrated that hormone receptors sites, that act as supromolecular hosts, non-covalently bind organometallic pharmaceuticals via specific H-bonding, π-π, and CH-π interactions, while modifying the conformation of helical proteins at the receptor site that must have a profound effect on biological activity for breast cancer

therapy. This chapter represents new vistas in the bioorganometallic chemistry discipline, focused on supramolecular host structural diversity and molecular recognition studies, and we are hopeful that we have been able to enlighten the organometallic community to these new directions, and to envision the exciting possibilities for future directions. Clearly, as organometallic chemists, we have a vital role at the interface of chemistry and biology to create new paradigms for basic research and, for example, medical applications, for the betterment of the global society.

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